Cardiac Stem Cell Niches

Annarosa Leri

Cardiovascular Research Institute, Department of Medicine, New York Medical College, Valhalla, NY

According to the accepted paradigm, the heart survives and exerts its function until death of the organism with the same cells that are present at birth. This notion has been challenged by findings documenting the activation of cyclins, cdks, BrdU incorporation, and the expression of Ki67, MCM5, Cdc6, and phospho-histone H3 in myocyte nuclei. The identification of the mitotic spindle and contractile ring during karyokinesis and cytokinesis has further demonstrated the existence of a subpopulation of replicating myocytes. However, the search for the origin of dividing myocytes was unsatisfactory until a population of primitive cells with the characteristics of stem cells was shown in the heart of humans and animals. Cardiac stem cells (CSCs) are lineage negative cells that express the SC antigens, c-kit, MDR1, and Sca-1, alone or in variable combinations. CSCs possess the properties of stemness: clonogenicity, self-renewal, and multipotentiality. When CSCs are implanted in the infarcted heart, they engraft, grow, and differentiate, replacing the dead tissue with new contracting myocardium.

If cardiac stem cells (CSCs) exist, they must take long-term residence in the heart. The adult heart contains interstitial structures with the architectural organization of stem cell niches. The number and size of the niches are greater in the atria and apex and lower at the base-mid region of the LV. These quantitative differences correlate with the regional differences in the function of the heart. The atria constitute the cardiac compartment exposed to minimal levels of myocardial stress, while the base-mid-region of the left ventricle is responsible for most of the pump performance of the heart. The apex is exposed to negligible working demands and mechanical stimuli. Cardiac niches contain clusters of CSCs and early lineage committed cells together with supporting cells represented by myocytes and fibroblasts. Connexins and cadherins are found between CSCs, early lineage committed cells, and supporting cells. The undifferentiated state of CSCs is associated with the expression of the α_4-integrin subunit that co-localizes with α_2-chain of laminin and fibronectin. Within the niches, CSCs divide symmetrically and asymmetrically. The uncommitted property of daughter cells is preserved by the degradation of the Notch receptor by Numb and α-adaptin. Conversely, active Notch promotes the formation of a differentiated progeny. BrdU pulse-chase assays demonstrate that cardiac niches harbor a subset of label retaining cells. Thus, the heart is a self-renewing organ in which cardiac homeostasis is regulated by stem cells located in niches.